Neonatal Hyperbilirubinemia

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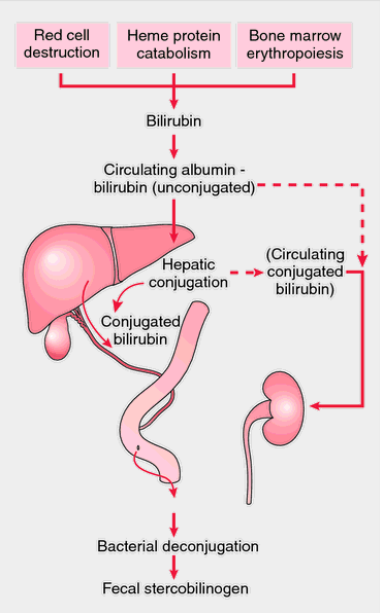
Definition: Hyperbilirubinemia is one of the most common problems encountered in newborns. Jaundice is observed during the first week of life in approximately 60% of term infants and 80% of preterm infants. It results from the deposition of unconjugated bilirubin pigment in the skin and mucus membranes. ***Hyperbilirubinemia is defined as a total serum bilirubin level greater than 5 mg/dL.***

Differential Diagnosis:

Unconjugated Hyperbilirubinemia (CB < 15% of TB)	Conjugated Hyperbilirubinemia (CB >15% of TB)

• Physiologic jaundice
  o Breastfeeding jaundice (first week)
  o Breastmilk jaundice (second week)
• Hemolysis
  o ABO incompatibility
  o Rh incompatibility
• RBC enzyme/membrane defects
  o G6PD deficiency
  o Pyruvate kinase deficiency
  o Hereditary spherocytosis
  o Hereditary elliptocytosis
• Conjugation defects
  o Gilbert disease
  o Crigler-Najjar syndrome
• Other
  o Sepsis
  o Galactosemia
  o Pyloric stenosis
  o Cephalohematoma or bruising
  o PC 2/2 delayed cord clamping
	• SEPSIS!
	• Extrahepatic biliary obstruction
	  o Biliary atresia
	  o Choledocal cysts
	  o Tumors/masses
	  o Neonatal sclerosing cholangitis
	• Metabolic/genetic diseases
	  o Hypothyroidism
	  o Hypopituitarism
	  o Galactosemia
	  o Alagille syndrome
	  o Alpha-1 antitrypsin deficiency
	  o Cystic fibrosis
	  o Maternal diabetes
	• Toxins
	  o Drugs (aspirin, acetaminophen, rifampin, alcohol, corticosteroids)
	• Cholestasis associated with TPN
	• Neonatal hepatitis

Life Cycle of Bilirubin: It might easier to understand the pathophysiology of hyperbilirubinemia if one can visualize the normal life cycle of bilirubin:

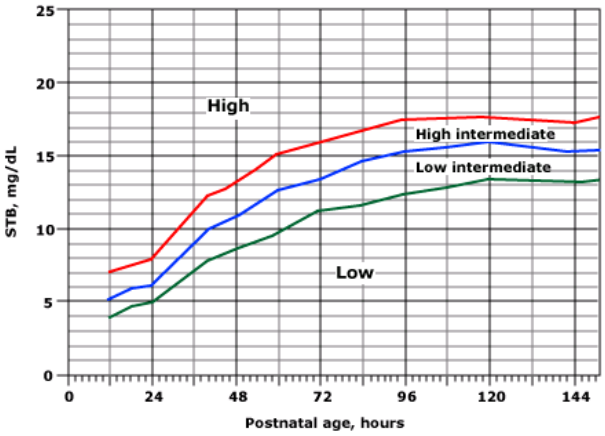


- Bilirubin is a product of heme catabolism; it is broken down in two steps (not shown in diagram)
  - Heme → CO2 + biliverdin (via heme oxidase)
  - Biliverdin → unconjugated bilirubin (via biliverdin reductase)
- Bound to albumin, circulating bilirubin is taken to the liver where it is conjugated by the enzyme UGT. This conjugated bilirubin is more water-soluble and is excreted as bile in to the intestinal lumen.
- Differences in neonates:
  - Bilirubin production is 2-3 times higher than in adults 2/2 increased HCT and greater RBC turnover (85 vs. 120 days).
  - Decreased conjugation due to decreased activity of UGT enzyme (does not reach adult levels until 14 weeks).
  - Increased enterohepatic circulation due to sterility of infant gut and reduced gut motility.
- For these reasons, all infants have some degree of physiologic jaundice
  - Mean peak TB occurs 48-96 hours of age and is 7-9 mg/dL
  - Primary neonatal jaundice usually resolves in 1-2 weeks

When to Worry: Although all infants do have some degree of physiologic jaundice, it is important to realize when to be concerned about severe hyperbilirubinemia. The following are signs of severe hyperbilirubinemia that need to be addressed:

1) Visible jaundice in the first 24 hours which is usually caused by increased bilirubin production due to severe hemolysis.
2) Total bilirubin greater than the 95th% for the hour of life (see right). The risk can be quantified using the newborn hyperbilirubinemia assessment calculator.
3) Rate of TB rise is > 0.2 mg/dL/hour.
4) Persistent jaundice in a term infant after 2 weeks of age.
5) Direct bilirubin > 1.0 (if TB <5) or ≥ 20% of total bilirubin.

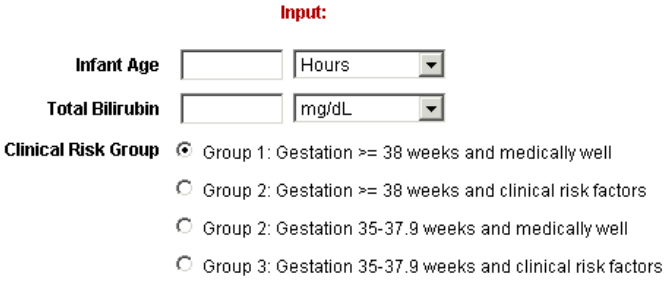
Bhutani Nomogram



Labs to order/actions to consider:

- TB with fraction (to determine type of hyperbilirubinemia)
- CBC + smear (to r/o RBC membrane defect)
- Type + Coombs (to determine RBC incompatibility or autoimmune hemolysis)
- Retic count (to determine rate of turnover)
- G6PD + PK assay if high suspicion
- Monitor infant closely with serial bilirubin checks
- Consider treatment (see below)

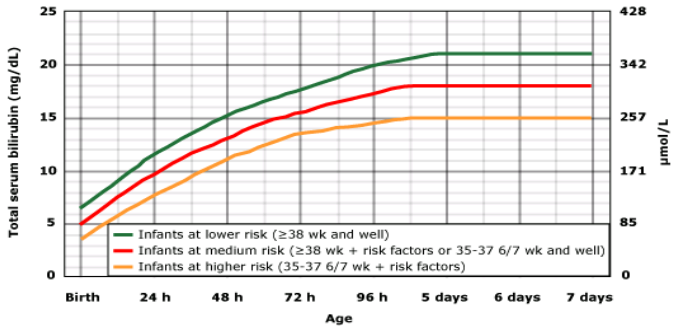
Newborn Hyperbilirubinemia Assessment Calculator



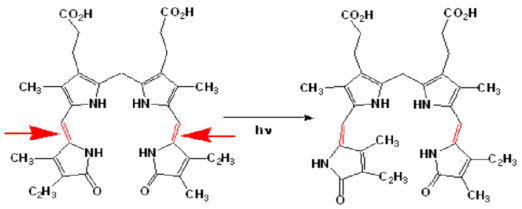
Treatment: The need for treatment has been changed drastically due to the widespread use of RhoGAM, decreasing the incidence of incompatibility hemolysis. However, there are still 3 interventions used to treat severe hyperbilirubinemia:

Phototherapy: using a specific wavelength of light, phototherapy converts unconjugated bilirubin to the more water soluble lumirubin, a less toxic bilirubin isomer, or to a more polar compound that can be excreted in the urine. For bilirubin levels > 20 mg/dL, phototherapy should be administered continuously until levels fall below 20 mg/dL, upon which it can be administered intermittently. Specific guidelines for phototherapy depend on the hour-specific TB level (see below). Since urinary excretion is the main mechanism by which phototherapy reduces TB levels, it is important to maintain adequate hydration to ensure proper urine output. Phototherapy is generally discontinued when TB levels reach 14 mg/dL. If phototherapy fails or infants are already showing signs of BIND (bilirubin-induced neurologic dysfunction), an immediate type and cross should be sent and the infant should be admitted to the NICU for immediate exchange transfusion.

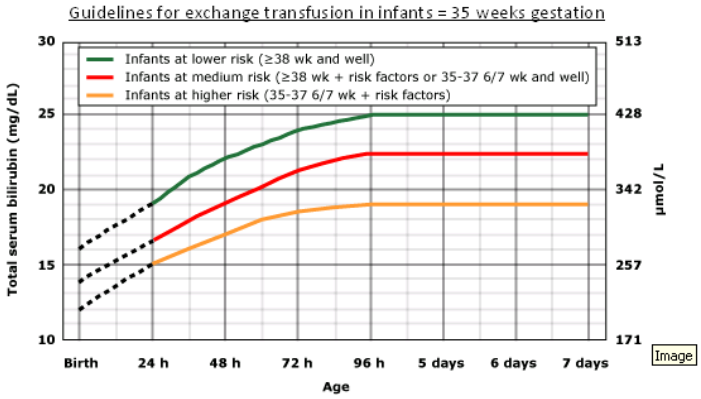
Guidelines for phototherapy in infants ≥ 35 weeks gestation



Conversion of unconjugated bilirubin to a more water soluble compound



Exchange Transfusion: used as treatment after phototherapy fails, it is the most effective means to rapidly remove bilirubin from circulation, especially when there are already visible signs of BIND. With the use of RhoGAM and the increased efficacy of phototherapy, it is used much less than before. Exchange transfusion is especially useful in infants with increased TB 2/2 immune hemolysis as the circulating antibodies and sensitized RBCs are also removed. Indications for its use include any jaundiced infant with clinical signs of BIND (lethargy, hypotonia, poor-sucking, high pitched cry), or infants with a TB level greater than the threshold defined by the AAP. After a successful procedure, TB initially falls to half its pre-transfusion value and eventually equilibrates at two-thirds of this initial level.



Pharmacologic Treatment: of the following, only IVIG is currently used to treat unconjugated hyperbilirubinemia.

- *IVIG:* can reduce the need for exchange transfusion in infants with hemolytic disease caused by Rh or ABO incompatibility. The mechanism is uncertain, but it is thought to inhibit hemolysis by blocking antibody receptors on RBC. It is indicated if TB levels are within 2-3 mg/dL of the threshold for transfusion.

- *Phenobarbital:* increases the conjugation and excretion of bilirubin. Prenatal administration may adversely affect cognitive development. As a result, it is not routinely used for treatment.

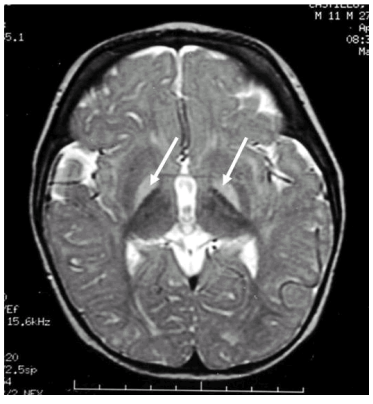
- *Ursodeoxycholic acid:* increases bile flow and is useful in the treatment of cholestatic jaundice.

Outcome and Complications: when neonates are identified and treated appropriately, the outcome of hyperbilirubinemia is usually excellent, with no long-term neurologic sequelae. However, failure to intervene early could lead to several adverse consequences. Bilirubin is a neurotoxin and neurotoxicity becomes evident when TB levels ≥25 mg/dL. At these levels, indirect bilirubin can pass through the blood-brain barrier and produce irreversible damage via apoptosis and necrosis. The brain regions most affected are the basal ganglia, hippocampus, and the brainstem nuclei for occulomotor and auditory function. Adverse clinical complications can be categorized based on timeline:

- Acute Bilirubin Encephalopathy: ABE describes the acute manifestations of neurologic dysfunction and can be reversible if corrected early enough. It progresses through three stages:
  - In the early phase, the clinical signs are subtle: the infant is sleepy and may have hypotonia or a high-pitched cry.
  - The intermediate phase involves persistence of the hyperbilirubinemia; the infant can be febrile, lethargic with a poor suck, irritable, and begin to show signs of retrocollis or opisthotonus.
  - The advanced phase is characterized by apnea, inability to feed, fever, seizures, persistent hypertonicity, and a weak cry. Death is usually due to respiratory failure or intractable seizures.

- Kernicterus: this is the chronic and usually permanent sequelae of BIND that develops after the first year. Cognitive function is usually spared. The major features include:
  - Choreoathtoid cerebral palsy (chorea, ballismus, tremor, dystonia)
  - Sensorineural hearing loss
  - Gaze abnormalities, especially limitation of upward gaze
  - Dental enamel dysplasia

  MRI of the head identifies localization of kernicterus ⟶
  (hyperintense basal ganglia lesions on T2-weighted images)



Prevention and Risk Factors: as with most other diseases, the best treatment is prevention in the first place. The following are some effective measures to prevent neonatal hyperbilirubinemia, and risk factors to be wary of while evaluating newborns:

- Initiate successful breastfeeding: This is done via observation and education of mothers in the nursery. Mothers should feed whenever the baby is hungry, or whenever 4 hours have elapsed since the last feed. Ideally, one should be feeding every 2-3 hours, no more than 15-20 minutes duration during each round of feeding. The goal is 8-12 feeds per day.

- Routine bilirubin monitoring: Mothers are screened prenatally for blood type and antibodies and should receive RhoGAM in the appropriate clinical circumstance. Neonates should be screened for risk factors (below) and all infants should have TB checked by 24 hours of life and at discharge. All values should be plotted on the Bhutani Nomogram to assess risk. Infants should be assessed visually for jaundice every 8-12 hours. Infants with above high risk levels should either have phototherapy initiated or should have guaranteed PCP follow-up within 24 hours of discharge.

- Short-term PCP follow-up: All infants should be seen within 3-4 days of hospital discharge, at the latest. At that visit, if the infant has lost more than 10% of the birth weight, is not urinating/stooling appropriately, or if the mother does not feel that there is adequate milk letdown, brief formula supplementation may be recommended.

In the weeks after birth it is also important to distinguish between the different types of jaundice that may arise:

- Breastfeeding jaundice: typically occurs during the first week of life with increased bilirubin levels and is usually related to suboptimal milk intake. Poor intake leads to weight loss, dehydration and decreased passage of stool, with resultant decreased excretion of bilirubin in the stool.

- Breast milk jaundice: typically occurs after the first week of life and is likely related to breast milk's high levels of β-glucuronidase and high lipase content. This elevated enzyme level increases intestinal deconjugation and resorption of bilirubin. Elevated bilirubin is highest in the second and third weeks of life, and lower levels may persist until 10 weeks of life.

Major Risk Factors	***Minor Risk Factors***	***Decreased/Negative Risk Factors***
• Predischarge TB levels in high-risk zone • Jaundice observed in first 24 hours • Blood group incompatibility with +DAT, or other known hemolytic disease • Gestational age 35-36 weeks • Previous sibling receiving phototherapy • Cephalohematoma or significant bruising • Exclusive breastfeeding • East Asian race	• Predischarge TB levels in the high intermediate-risk zone • Gestational age 37-38 weeks • Jaundice observed before discharge • Previous sibling with jaundice • Macrosomic infant of diabetic mother • Maternal age≥ 25 years • Male gender	• TB levels in the low-risk zone • Gestational age ≥41 weeks • Exclusive bottle feeding • Black race • Discharge from hospital after 72 hours

References:

Multiple primary sources and figures were obtained and used from the following Up-to-Date articles (accessed on 5/20/11):

1) Up-to-Date: “Pathogenesis and etiology of unconjugated hyperbilirubinemia in the newborn”
2) Up-to-Date: “Evaluation of unconjugated hyperbilirubinemia in term and late preterm infants”
3) Up-to-Date: “Treatment of unconjugated hyperbilirubinemia in term and late preterm infants”
4) Up-to-Date: “Clinical manifestations of unconjugated hyperbilirubinemia in term and late preterm infants”
5) Up-to-Date: “Causes of neonatal cholestasis”
6) Up-to-Date: “Approach to neonatal cholestasis”
7) Up-to-Date: “Bilirubin metabolism”

8) BRS Pediatrics; Lloyd Brown and Lee Miller. 2005.
9) “AAP Clinical Practice Guideline: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation.” Pediatrics vol. 114 No. 1 July 2004, pp. 297-316.
10) Website: “http://en.wikipedia.org/wiki/Kernicterus.” Accessed on 5/20/11.
11) Website: “http://medical-dictionary.thefreedictionary.com/Total+bilirubin.” Accessed on 5/20/11.
12) Website: “http://en.domotica.net/Crigler%E2%80%93Najjar%20syndrome.” Accessed on 5/20/11.
13) Website: “http://pedclerk.bsd.uchicago.edu/.” Accessed on 5/23/11.
14) Lecture: Lauren Conti, MD, Chief Resident of Pediatrics, on 5/4/11.